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Hepatic artery infusion chemotherapy combined with camrelizumab and apatinib as conversion therapy for patients with unresectable hepatocellular carcinoma: a single-arm exploratory trial

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Abstract

Background The development of systemic therapy, including targeted drugs and immune checkpoint inhibitors, has significantly improved the prognosis of patients with advanced unresectable hepatocellular carcinoma (uHCC). Hepatic arterial infusion chemotherapy (HAIC) has been gradually applied to the treatment of advanced uHCC, showing good potential as conversion therapy. We aimed to investigate the efficacy and safety of HAIC combined with camrelizumab and apatinib as conversion therapy for uHCC.

Methods This study was a single-arm exploratory trial (NCT05099848) in patients with uHCC. Eligible patients received apatinib 250 mg once daily, camrelizumab 200 mg on day 3, and HAIC with FOLFOX regimen (oxaliplatin 85 mg/m^2 at hours 0–2, leucovorin 400 mg/m^2 at hours 2–3, and fluorouracil 400 mg/m^2 at hour 3, followed by fluorouracil 2400 mg/m^2 for 46 h) on days 4–5 of each 21-day cycle for up to 8 cycles. Primary endpoints were conversion rate and margin-free (R0) resection rate.

Results Between March 2021 and July 2023, 19 patients were enrolled. Median follow-up was 14.9 months (interquartile range, 10.9–21.1). Disease became resectable in 14 (73.7%) of 19 patients; nine (47.4%) patients received R0 resection, while five (26.3%) refused surgery and opted for observation. Three (33.3%) of nine patients with surgery achieved major pathological response, including two (22.2%) with pathological complete response. Objective response and disease control rates were 47.4% (9/19) and 89.5% (17/19) per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 and both 89.5% (17/19) per modified RECIST. Survival data were immature. Fourteen (73.7%) of 19 patients had grade 3 or higher treatment-related adverse events, with the most common being

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increased alanine aminotransferase or aspartate aminotransferase (seven [36.8%]) and increased lymphocyte count (six [31.6%]). No treatment-related deaths occurred.

Conclusions The combination of HAIC, camrelizumab, and apatinib as conversion therapy shows promising clinical benefits and a manageable safety profile in patients with uHCC. Future randomized controlled trials are warranted.

Trial registration ClinicalTrials.gov NCT05099848. Registered on October 13, 2021.

Keywords Apatinib, Camrelizumab, Hepatic arterial infusion chemotherapy, Unresectable hepatocellular carcinoma, Conversion therapy

Background

Primary liver cancer is a common malignant tumor in the digestive system that seriously affects human health, ranking sixth in incidence and third in mortality among all malignant tumors. In China, hepatocellular carcinoma (HCC) accounts for 75–80% of primary liver cancer cases [1]. Surgical resection and liver transplantation are the main curative treatments for HCC at present, and are the most important approaches for patients to achieve long-term survival. However, it is difficult to diagnose HCC at early stage due to the lack of typical clinical symptoms. More than 80% of patients are diagnosed at advanced stage and are unable to undergo radical resection. The 5-year overall survival (OS) rate is only 10%−18% [2, 3]. Currently, the main drugs approved for the first-line treatment of advanced HCC include sorafenib, lenvatinib, and atezolizumab combined with bevacizumab.

Apatinib (also known as rivoceranib) is a tyrosine kinase receptor inhibitor that selectively targets vascular endothelial growth factor receptor-2 to inhibit tumor-induced angiogenesis. It has shown synergistic anti-tumor effects when combined with camrelizumab (anti-programmed cell death-1 [PD-1] antibody) in patients with advanced HCC [4]. In a randomized, open-label, international phase 3 study (CARES-310), the median progression-free survival (PFS; 5.6 months vs 3.7 months; hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.41–0.65) and OS (22.1 months vs 15.2 months; HR, 0.62; 95% CI, 0.49–0.80) were significantly improved with camrelizumab plus apatinib compared to sorafenib. In China, camrelizumab plus apatinib has also been approved for the first-line treatment of advanced HCC [5].

In recent years, hepatic artery infusion chemotherapy (HAIC) has been gradually applied to the treatment of advanced HCC, showing good potential as conversion therapy [6]. He et al. conducted a phase 3 trial to compare the efficacy and safety of sorafenib plus HAIC with sorafenib monotherapy in treating HCC patients with portal vein invasion. The results showed that sorafenib plus HAIC nearly doubled the median OS (13.4 months vs 7.1 months; HR, 0.35; 95% CI, 0.26–0.48) and improved the objective response rate (ORR; 40.8% vs 2.5% per Response Evaluation Criteria In Solid Tumors [RECIST] version 1.1; 54.4% vs 5.7% per modified RECIST [mRECIST]) compared with sorafenib monotherapy, with a manageable safety profile [7]. In a retrospective comparative study reported by Deng et al., the ORR and median PFS with HAIC conversion therapy for huge unresectable HCC (uHCC) were 44.3% and 8.9 months, respectively, significantly higher than those in patients who received transarterial chemoembolization [8].

Thus, this study aimed to evaluate the efficacy and safety of HAIC combined with camrelizumab and apatinib as a conversion therapy for patients with uHCC.

Methods

Study design and participants

This study was a single-arm, single-center exploratory trial (NCT05099848) conducted at Shandong Cancer Hospital Affiliated to Shandong First Medical University. Patients aged 18 to 80 years with uHCC who had Barcelona Clinic Liver Cancer (BCLC) B or C stage disease without extrahepatic metastasis were eligible for the study. According to the investigator's assessment, patients enrolled should be expected to achieve margin-free (R0) resection after conversion therapy, including but not limited to one of the following situations: (1) residual liver volume was less than 30% in patients without cirrhosis or less than 40% in patients with cirrhosis; (2) the number of tumor lesions was less than 3, and the lesions were mainly concentrated on one side of the liver; (3) imaging examination indicated portal vein tumor thrombus (PVTT); (4) other situations where radical resection might be feasible after conversion therapy, as judged by investigators. Other major inclusion criteria included Eastern Cooperative Oncology Group performance status of 0–1; Child–Pugh liver function class A; at least one measurable lesion according to RECIST 1.1; no diffuse multifocal tumors throughout the liver; and adequate cardiac, pulmonary, hepatic, renal, and hematopoietic function. Previous treatments (such as resection, radiofrequency ablation, percutaneous ethanol injection) at least 2 years prior to recurrence were allowed.

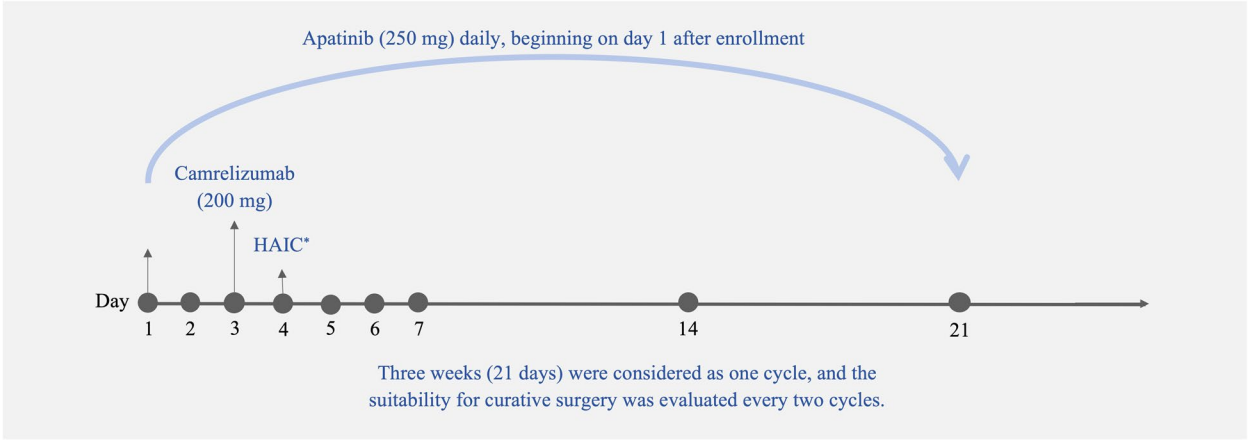

Fig. 1 The scheme of camrelizumab combined with apatinib and HAIC. *Hepatic arterial infusion chemotherapy

Invasion of the tumor into the branch portal vein and/or hepatic vein was allowed. Patients with severe comorbidities (e.g., symptomatic congestive heart failure, unstable angina, and uncontrolled hypertension) or a life expectancy of less than 3 months were excluded. Patients who had received immunotherapy in the past, had a history of allergy to the study drug or any other drug components, had any active autoimmune disease, or had a history of autoimmune disease were also excluded. A complete list of eligibility criteria can be found in the supplementary file 1. All patients provided written informed consent, and the Shandong Cancer Hospital Research Institute Ethics Committee approved the protocol (No. SDZLEC2021-021–01). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice standards.

Procedures

All patients received oral apatinib 250 mg once daily, intravenous camrelizumab 200 mg on day 3, and HAIC with FOLFOX regimen (oxaliplatin 85 mg/m^2 at hours 0–2, leucovorin 400 mg/m^2 at hours 2–3, and fluorouracil 400 mg/m^2 at hour 3, followed by fluorouracil 2400 mg/m^2 for 46 h) on days 4–5 of each 21-day cycle for up to 8 cycles (Fig. 1). HAIC was performed by inserting a 5-French Rosch Hepatic catheter (Terumo Corporation, Tokyo, Japan) through the femoral artery with a 2.4 or 2.7-French microcatheter inside, and then, advancing the tip of the microcatheter to the tumor-feeding artery, guided by concurrent arteriography. The catheter and sheath were removed after the completion of each HAIC procedure.

During the study, enhanced magnetic resonance imaging or computed tomography scan was performed every 2 cycles (consistent with the baseline examination). Tumor response was evaluated by investigators according to RECIST 1.1 and mRECIST, respectively. Physical examinations and laboratory tests were performed before and after each treatment cycle. Disease resectability and treatment failure were discussed by a multidisciplinary team (including surgeons specializing in liver surgery, clinical oncologists, interventional radiologists, and diagnostic radiologists) every 2 weeks. Curative surgery would be performed in resectable patients at a scheduled time. Camrelizumab should be stopped for 1 month and apatinib should be stopped for 2–6 weeks before surgery. If patients still could not undergo curative surgery after completing 8 cycles of conversion therapy, they would receive any treatment at investigators' discretion. Follow-up would be continued in these unresectable patients until disease progression, intolerable toxicity, or withdrawal of informed consent.

Adverse events (AEs) were recorded throughout the treatment period and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Outcomes

The primary endpoints were conversion rate (defined as the proportion of patients who were deemed suitable for radical resection after conversion therapy) and R0 resection rate. Secondary endpoints were major pathological response (MPR) rate (defined as the proportion of patients with $\leq$10% residual tumor cells), ORR (defined as the proportion of patients with complete responses [CR] or partial responses [PR]), disease control rate (DCR; defined as the proportion of patients with CR, PR, or stable disease [SD]), PFS (defined as the time from the initiation of conversion therapy to disease progression or any-cause death), OS (defined as the time from the

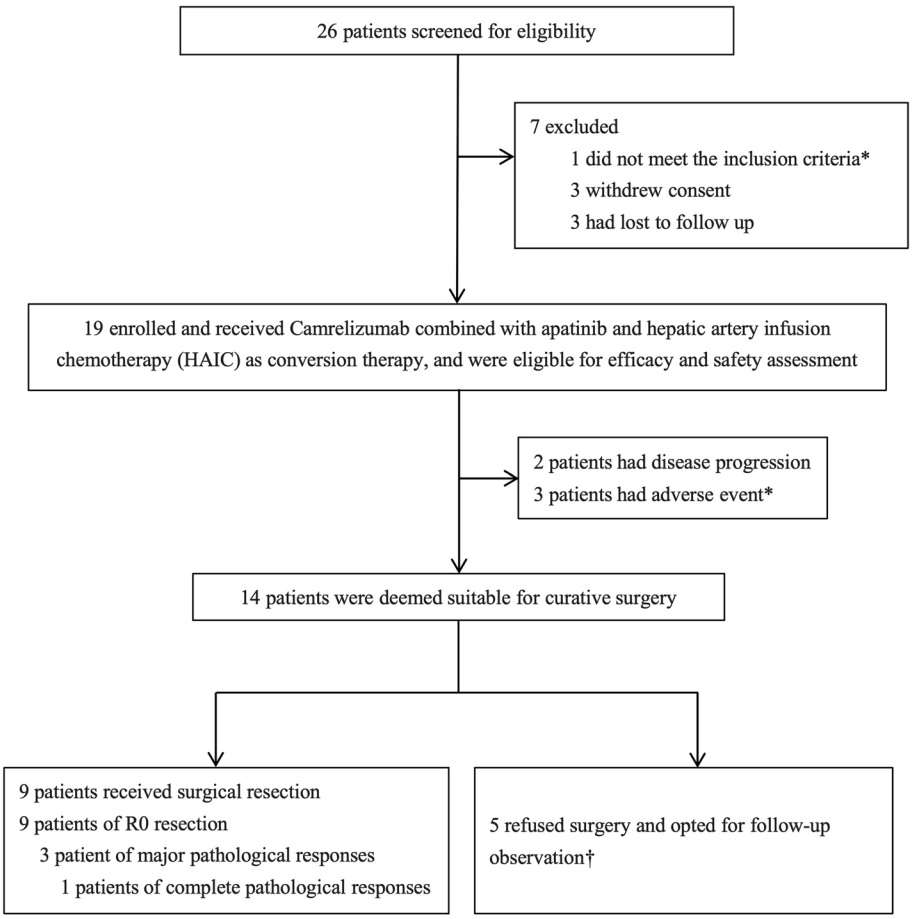

Fig. 2 Trial profile. *One patient experienced grade 4 hepatic dysfunction, one patient experienced grade 4 immune-mediated myocarditis, and one patient experienced grade 3 cerebral infarction. †Four patients achieved complete response, and one achieved partial response per modified Response Evaluation Criteria In Solid Tumors

initiation of conversion therapy to any-cause death), and safety.

Statistical analysis

Continuous variables were expressed as median (interquartile range [IQR]). Categorical variables were expressed as frequency (percentage). The 95% CIs of conversion rate, R0 resection rate, MPR rate, ORR, and DCR were estimated using the Clopper-Pearson method. PFS, OS, and DOR were estimated using the Kaplan–Meier method, and the corresponding 95% CIs were estimated using the Brookmeyer-Crowley method. A post-hoc analysis was performed for pathological complete response (pCR) rate (defined as the proportion of patients with no residual tumor cells), and the corresponding 95% CI was estimated using the Clopper-Pearson method. All the statistical analyses were performed using the IBM SPSS Statistics 26.0 (SPSS, Chicago, Illinois, USA) and GraphPad Prism 10.2.0 (GraphPad, San Diego, CA, USA).

Results

Between March 17, 2021, and July 25, 2023, a total of 26 patients were screened. However, one patient did not meet the eligibility criteria, three patients withdrew the informed consent, and three patients were lost to follow-up (Fig. 2). Overall, 19 patients were deemed eligible and received conversion therapy, which were included in efficacy and safety analyses. Baseline characteristics are presented in Table 1. Most of the patients were males (73.7%). Ten patients (52.6%) had vascular invasion and were classified as BCLC C stage (Table 2).

As of the data cut-off date (May 31, 2024), the median follow-up duration was 14.9 months (IQR, 10.9–21.1). The median number of conversion therapy cycles was 2.5 (IQR, 2.0–3.0). Five (26.3%) of 19 patients discontinued the conversion therapy. Among these five patients, two had disease progression and received standard second-line treatment, while the other three experienced AEs and received subsequent anti-tumor treatment after recovery from AEs. The remaining 14 patients

Table 1 Baseline characteristics of 19 converted HCC patients

Characteristics	Patients ($n=19$)
Median age, years (range)	56(41–76)
Sex	
Male	14(73.7%)
Female	5(26.3%)
Eastern Cooperative Oncology Group performance status	
0	14(73.7%)
1	5(26.3%)
Hepatitis B virus infection	17(89.5%)
Albumin-bilirubin score	
Grade 1	13(68.4%)
Grade 2	6(31.6%)
BCLC stage[a]	
A	7(36.8%)
B	2(10.5%)
C	10(52.6%)
CNLC stage[a]	
Ib	7(36.8%)
IIa	1(5.3%)
IIb	1(5.3%)
IIIa	10(52.6%)
Reasons for cancer being unresectable	
Vascular invasion	5(26.3%)
Inadequate liver remnant volume	9(47.4%)
Both	5(26.3%)
Liver cirrhosis	15(78.9%)
Number of lesions	
Solitary	12(63.2%)
Multiple	7(36.8%)
Median size of largest lesion, mm (IQR)	119.0(99.7–140.6)
AFP, ng/mL	
≤ 400 ng/mL	9(47.4%)
> 400 ng/mL	10(52.6%)
Previous treatment	
No	18(94.7%)
Yes (Resection)	1(5.3%)

Data are n (%) unless otherwise specified

BCLC Barcelona Clinic Liver Cancer, *NCLC* China Liver Cancer, *Vp2* invasion of (or tumor thrombus in) second order branches of the portal vein, *Vp3* invasion of (or tumor thrombus in) first order branches of the portal vein, *Vp4* invasion of (or tumor thrombus in) the main trunk of the portal vein and/or contra-lateral portal vein branch to the primarily involved lobe, *Vv3* invasion of (or tumor thrombus in) the inferior vena cava

[a] At time of registration

were deemed suitable for curative surgery after conversion therapy, with a conversion rate of 73.7% (95% CI, 48.6–89.9). Nine (64.3%) of these 14 patients underwent surgery, while five (35.7%) refused surgery and opted for observation. The R0 resection rate was 47.4% (9/19; 95% CI, 25.2–70.5) in the total population and 100% (9/9; 95% CI, 62.9–100) in patients with surgery. Three (15.8%; 95% CI, 4.2–40.5) of 19 patients achieved MPR, including two (10.5%; 95% CI, 1.9–34.5) patients with pCR (Table 3).

As per RECIST 1.1, nine patients achieved PR, with an ORR of 47.4% (95% CI, 25.2–70.5). Eight patients (42.1%) achieved SD, and the DCR was 89.5% (95% CI, 65.5–98.2). As per mRECIST, six patients (31.6%) achieved CR and 11 (57.9%) achieved PR, with an ORR of 89.5% (95% CI, 65.5–98.2). No patients achieved SD, and the DCR was also 89.5% (95% CI, 65.5–98.2; Table 3 and Fig. 3).

The median number of conversion therapy cycles for the six patients with CR per mRECIST was 3 (IQR, 3.0–4.0). One of these six patients underwent R0 resection, and achieved pCR. Four patients refused surgery and opted for observation. The remaining one patient had grade 4 hepatic dysfunction and could not undergo surgery. The median number of conversion therapy cycles for the 11 patients with PR per mRECIST was 3 (IQR, 2.8–3.0). Eight of these 11 patients underwent R0 resection, and two patients achieving MPR (including one with pCR). Two patients were unable to undergo surgery due to grade 3 cerebral infarction and grade 4 immune-mediated myocarditis. The remaining one patient opted for observation.

As of the data cutoff date (May 31, 2024), the median PFS and OS were not reached. The 1-year and 2-year PFS rates were 63.2% (95% CI, 38.6–82.8) and 55.3% (95% CI, 31.7–76.9), and the 1-year and 2-year OS rates were 73.7% (95% CI, 48.6–89.9) and 63.2% (95% CI, 38.6–82.8), respectively (Fig. 4). Among the nine patients who had disease progression, four developed intrahepatic metastasis, four developed progression of the primary lesions, and one developed extrahepatic metastasis (right atrium). The causes of seven deaths included disease progression ($n=5$), decompensated hepatic failure ($n=1$), and cancer cachexia ($n=1$).

Among the nine patients with surgery, three experienced recurrence (PFS: 4.9 months, 5.3 months, and 7.6 months) and two died (OS: 19.0 months and 26.9 months). The 1-year OS and 2-year OS rates were 100% and 66.7% for these nine patients, respectively. Of the five patients who refused surgery and opted for observation, three had disease progression (PFS: 9.6 months, 11.9 months, and 32.5 months), and two died (OS: 8.2 months each).

During the study period, all the 19 patients experienced treatment-related AEs (TRAEs; Table 4). Fourteen (73.7%) patients experienced at least one grade 3 or higher TRAE. The most common grade 3 or higher TRAEs were increased alanine aminotransferase or aspartate aminotransferase (seven [36.8%]) and increased lymphocyte count (six [31.6%]). Three (15.8%) patients discontinued the conversion therapy due to AEs (one

Table 2 The stage and reasons of unresectability of all patients ($n = 19$)

Patients	CNLC stage	BCLC stage	Reasons of unresectability
1	IIIa	C	Vp4
2	IIIa	C	Vp2, Inadequate liver remnant volume
3	IIIa	C	Vv3
4	IIa	B	Inadequate liver remnant volume
5	Ib	A	Inadequate liver remnant volume
6	Ib	A	Inadequate liver remnant volume
7	IIIa	C	Vp3, Inadequate liver remnant volume
8	IIIa	C	Vp3, Vv3, Inadequate liver remnant volume
9	IIIa	C	Vp3, Inadequate liver remnant volume
10	Ib	A	Inadequate liver remnant volume
11	IIIa	C	Vp1, Inadequate liver remnant volume
12	IIa	B	Inadequate liver remnant volume
13	IIIa	C	Vp3
14	Ib	A	Inadequate liver remnant volume
15	IIIa	C	Vp2
16	Ib	A	Inadequate liver remnant volume
17	IIIa	C	Vp2
18	Ib	A	Inadequate liver remnant volume
19	Ib	A	Inadequate liver remnant volume

BCLC Barcelona Clinic Liver Cancer, *NCLC* China Liver Cancer, *Vp1* invasion of (or tumor thrombus in) third order branches of the portal vein, *Vp2* invasion of (or tumor thrombus in) second order branches of the portal vein, *Vp3* invasion of (or tumor thrombus in) first order branches of the portal vein, *Vp4* invasion of (or tumor thrombus in) the main trunk of the portal vein and/or contra-lateral portal vein branch to the primarily involved lobe, *Vv3* invasion of (or tumor thrombus in) the inferior vena cava

grade 4 hepatic dysfunction, one grade 4 immune-mediated myocarditis, and one grade 3 cerebral infarction). Hepatic dysfunction and immune-mediated myocarditis were deemed related to the conversion therapy. Due to the acute onset of cerebral infarction, it was not possible to entirely attribute the event to the conversion therapy. All these AEs were manageable with symptomatic treatments. No treatment-related deaths occurred.

Discussion

Conversion therapy aims to transform the inoperable cancer into operable cancer through systemic therapy and/or local treatment, which can result in tumor shrinkage and local necrosis. As radical resection is the goal of HCC treatment, conversion therapy has become a hot topic in the treatment of advanced HCC [9], but its clinical application is still lacking in experience and evidence.

In our study, 73.7% (14/19) of patients were deemed suitable for curative surgery after conversion therapy with HAIC plus camrelizumab and apatinib. This conversion rate was similar with some previous studies [10–14]. In addition, the R0 resection rate was 47.4% (9/19), slightly higher than that in a phase 2 trial of lenvatinib combined with anti-PD-1 antibody (32.1%) as conversion therapy for uHCC [15]. It is worth noting that all patients who underwent surgery in our study achieved R0 resection.

Table 3 Assessment of objective response

Variable, n (%)	$n = 19$	
	RECIST v1.1	mRECIST
Objective response rate[a]	9 (47.4%)	17 (89.5%)
Complete response	0	6 (31.6%)
Partial response	9 (47.4%)	11 (57.9%)
Stable disease	8 (42.1%)	0
Progressive disease	2 (10.5%)	2 (10.5%)
Disease control rate[b]	17 (89.5%)	17 (89.5%,)
Conversion rate	14 (73.7%)	
R0 resection	9 (47.4%)	
Major pathologic response	3 (15.8%)	
Pathologic complete response	2 (10.5%)	

Data are n (%) unless otherwise stated

RECIST Response Evaluation Criteria in Solid Tumours

[a] Complete response or partial response

[b] Complete response, partial response, or stable disease for at least 8 weeks

The ORR was 47.4% per RECIST 1.1. The 1-year and 2-year PFS rates were 63.2% and 55.3%, and the 1-year and 2-year OS rates were 73.7% and 63.2%, respectively. According to the current international guidelines, BCLC C-stage patients are not suitable for local treatment due to poor prognosis caused by vascular invasion, but 52.6%

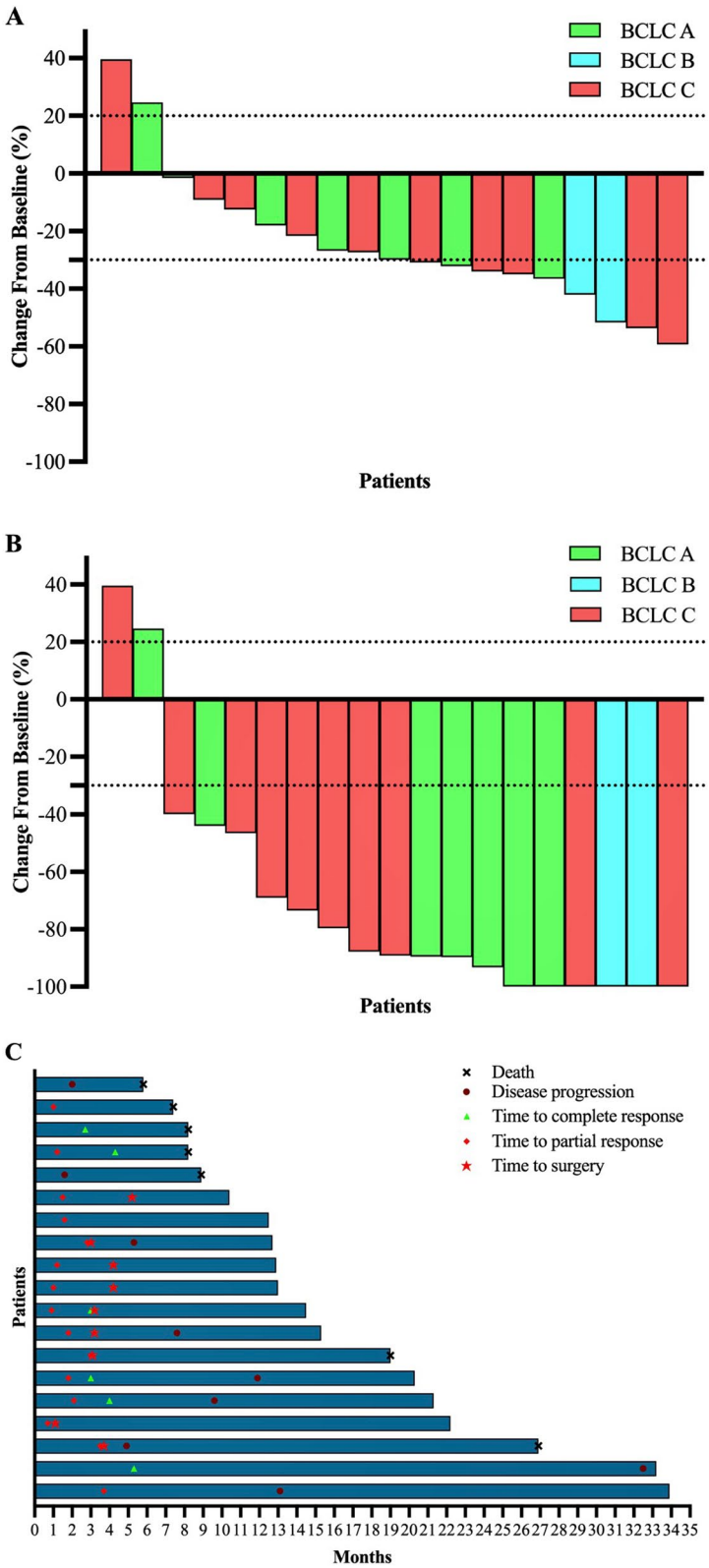

Fig. 3 Tumor response. Waterfall plot showing the percent change from baseline in the sum of the longest diameter of target lesions in each of the 19 patients, according to RECIST 1.1 (**A**) and modified RECIST (**B**). Swimmer plot showing the duration of response and time to response (**C**). Dashed lines in panels **A** and **B** represent partial response and progressive disease per RECIST 1.1 and modified RECIST, respectively. Blue bar in panel **C** indicates follow-up time. RECIST, Response Evaluation Criteria In Solid Tumors

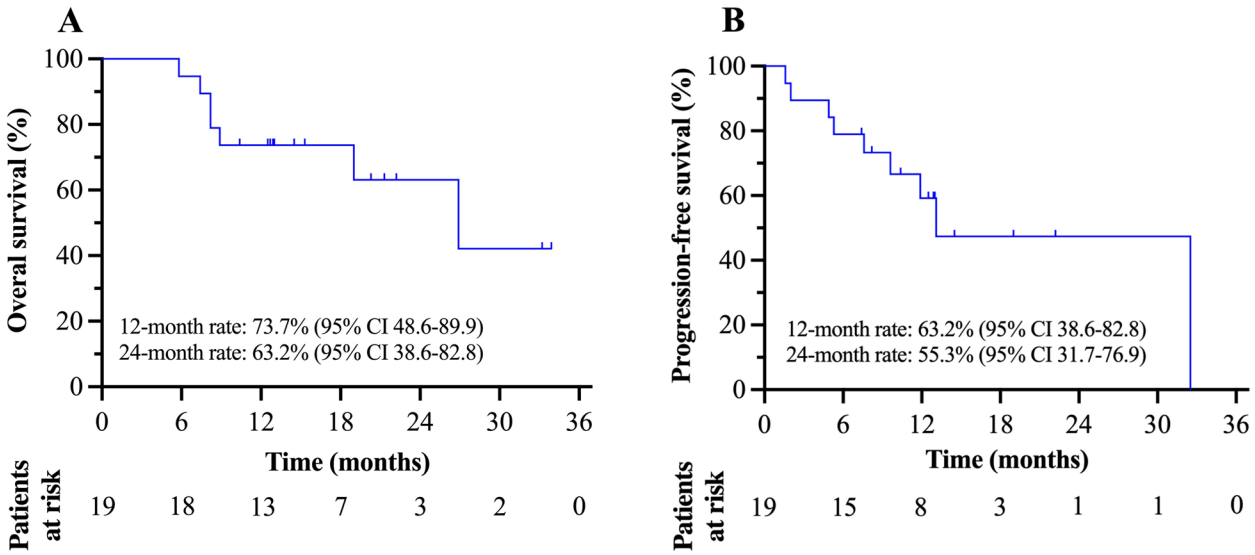

Fig. 4 Survival outcomes. OS, overall survival; PFS, progression-free survival

of the patients in our cohort had BCLC C-stage disease. Combined with recent studies, multi-modality therapy may bring better tumor response and survival benefit for patients with uHCC [16–19].

When analyzing survival outcomes in our study, all enrolled patients were included, comprising: (1) patients whose disease achieved conversion to resectable status but did not undergo surgery, (2) patients with unsuccessful conversion therapy, and (3) patients who underwent surgical resection after successfully conversion therapy. The 1-year and 2-year OS rates (73.7% and 63.2%) were within the range reported in previous studies of conversion therapy for uHCC (65.6%–80.4% [8, 19–22] and 51.6%–69.0% [8, 19]). For the nine patients with surgery after conversion therapy, the 1-year OS rate was 100%, consistent with our previous report in the surgery population (100%) [23]. However, due to the small sample size in our study, a large-scale randomized controlled trial is warranted to further validate the effect of HAIC combined with camrelizumab and apatinib on long-term survival outcomes.

The development of anti-angiogenic drugs and immunotherapy has significantly changed the treatment landscape of HCC [24]. Apatinib can induce vascular normalization, reduce tumor hypoxia and acidosis, and reprogram the tumor microenvironment [25]. Immune checkpoint inhibitor can activate cytotoxic T lymphocyte function, thus improving anti-tumor immunity. The chemotherapeutic drugs used in the FOLFOX regimen can induce tumor cell deaths and release tumor antigens [12, 26, 27], which may further enhance the effect of immune checkpoint inhibitors on eradicating occult metastasis [19, 25]. It is worth noting that the ORR per RECIST 1.1 in our study was lower than that in the phase 2 TRIPLET trial (47.4% vs 77.1%) [24], which used the same drug combination (with different doses and administration order) to treat BCLC C-stage uHCC. This might be explained by the differences in study purpose and endpoint criteria. The TRIPLET study used this regimen as first-line treatment, while we focused on conversion therapy. In our study, patients would be recommended to undergo curative surgery as long as they were deemed suitable after conversion therapy. We did not wait until the lesions shrunk to the minimal size. Even though this shrinkage did not meet the criteria of PR according to RECIST 1.1, the residual liver volume increased. Conversion therapy can bring opportunity for surgery and preserve more liver parenchyma [28, 29].

All patients experienced TRAEs during the study period. Of the 19 patients, 14 (73.7%) experienced at least one grade 3 or higher TRAE, with hepatotoxicity and myelosuppression being the most common. This incidence was consistent with that in the TRIPLET and RESCUE studies [4, 24]. Zuo et al. [23] reported that the incidence of grade 3 or higher AEs was 82.1% for HAIC plus camrelizumab and apatinib and 71.3% for camrelizumab plus apatinib. The increased incidence of hepatotoxicity and myelosuppression might be attributed to potential adverse effects associated with the infusion procedure [30, 31]. No treatment-related deaths occurred. Regarding the safety of conversion surgery, the results of our previous retrospective study [23] showed that the profile of surgical complications in patients undergoing surgery after conversion therapy was generally consistent with that in patients undergoing direct surgery during the

Table 4 Treatment-related adverse events

	Any-grade	High-grade[a]
Constitutional		
Fever	4(21.1%)	0
Abdominal pain	4(21.1%)	1(5.3%)
Skin		
Pruritus	1(5.3%)	0
Hand-foot skin reaction	1(5.3%)	0
Reactive cutaneous capillary endothelial proliferation	1(5.3%)	0
Gastrointestinal		
Decreased appetite	3(15.8%)	0
Nausea	2(10.5%)	0
Diarrhoea	3(15.8%)	0
Abdominal distention	2(10.5%)	0
Fecal occult blood	3(15.8%)	0
Hepatic		
Alanine aminotransferase increased	13(68.4%)	4(21.1%)
Aspartate aminotransferase increased	14(73.7%)	7(36.8%)
Gamma-glutamyl transferase increased	5(26.3%)	1(5.3%)
Bilirubin increased	12(63.2%)	1(5.3%)
Alkaline phosphatase increased	8(42.1%)	0
Creatine kinase increaased	6(31.6%)	0
Lactate dehydrogenase increased	18(94.7%)	0
Albumin decreased	18(94.7%)	0
Amylase increased	4(21.1%)	2(10.5%)
Renal		
Hypercreatinine	1(5.3%)	0
Proteinuria	6(31.6%)	0
Laboratory		
Anaemia	9(40.9%)	0
Leukopenia	13(68.4%)	3(15.8%)
Neutropenia	12(63.2%)	2(10.5%)
Hypolymphocytosis	18(94.7%)	6(31.6%)
Thrombocytopenia	12(63.2%)	1(5.3%)
Hyponatraemia	13(68.4%)	0
Hypokalaemia	6(31.6%)	0
Fibrinogenopenia	3(15.8%)	1(5.3%)
Hypersensitive troponin T increased	2(10.5%)	1(5.3%)
Immune-related		
Hypothyroidism	1(5.3%)	0
Hyperthyroidism	1(5.3%)	0
Myocarditis	1(5.3%)	1(5.3%)
Others		
Cerebral infarction	1(5.3%)	1(5.3%)

Data are n (%) of 19 patients

[a] Grade 3 or grade 4

same period. Data from our phase Ib study [32] of neoadjuvant therapy for early stage HCC also showed that preoperative neoadjuvant immunotherapy combined with SBRT therapy did not increase the incidence of surgical complications. However, given the high TRAE rate, active monitoring for AEs was still necessary when using this conversion therapy regimen. Whether these events would indirectly impact patient survival requires further investigation.

This trial has several limitations. First, the lack of a control group in our single-arm design made it difficult to attribute the observed benefits solely to the addition of systemic therapy. Second, the limited sample size in this study precluded statistical analysis. Third, 89.5% of patients had chronic hepatitis B, thus our study results may not be easily applicable to patients with different etiologies. Fourth, one patient with recurrent HCC who had relapsed after initial treatment were included in the efficacy analysis. The disease course of this patient might be different from that of untreated patients. The low participation rate of female patients (26.3%) may also affect the generalizability of our study results [19].

Conclusions

In conclusion, HAIC combined with camrelizumab and apatinib shows promising conversion rate and the potential to prolong OS benefit in patients with uHCC. The safety profile was manageable. Further large-scale randomized controlled trials are warranted to validate our findings.

Abbreviations

AE	Adverse event
BCLC	Barcelona Clinic Liver Cancer
CI	Confidence interval
CR	Complete responses
DCR	Disease control rate
HAIC	Hepatic artery infusion chemotherapy
HCC	Hepatocellular carcinoma
HR	Hazard ratio
IQR	Interquartile range
MPR	Major pathological response
mRECIST	Modified Response Evaluation Criteria In Solid Tumors
ORR	Objective response rate
OS	Overall survival
pCR	Pathological complete response
PD-1	Programmed cell death-1
PFS	Progression-free survival
PR	Partial responses
PVTT	Portal vein tumor thrombus
RECIST	Response Evaluation Criteria In Solid Tumors
R0	Margin-free
SD	Stable disease
TRAE	Treatment-related adverse event
uHCC	Unresectable hepatocellular carcinoma

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14250-5.

Supplementary Material 1.

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Authors' contributions
L.Z. conceived and designed the study. K.Y. and Z.C.L. performed data analysis and drafted the manuscript. L.Z., K.Y. and Z.C.L. interpreted the data. Z.G.L., L.L. C.S.Z., P.F.S., J.T.Z., K.C., X.T.S. and B.Z. contributed to patient recruitment and provision of study materials. J.X.Z., Z.B.C., M.M.L., Z.C.S., Y.Y. and L.X collected and assembled the data. All authors participated in critical revision of the article for intellectual content. All authors read and approved the final version of the manuscript.

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Data availability
Clinical data are not publicly available due to involving patient privacy, but can be accessed from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
All patients provided written informed consent, and the Shandong Cancer Hospital Research Institute Ethics Committee approved the protocol (No. SDZLEC2021-021–01).

Consent for publication
Not applicable.

Competing interests
L.Z. is on the speakers' bureau for Bayer, MSD, AstraZeneca, Roche, BeiGene, Innovent, Junshi Biosciences and Jiangsu Hengrui Pharmaceuticals. The remaining authors declare no competing interests.

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